Intravaginal Isosorbide Mononitrate and Misoprostol Versus Misoprostol Alone For Induction Of Labour

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Abstract:
Background: Induction implies stimulation of uterine contractions before the onset of labour with or without ruptured membranes, a process that generally employs prostaglandins to soften and open the cervix. Cervical ripening is necessary for cervical dilatation and commonly used to enhance the rate of successful labour induction. Prostaglandins are used commonly for ripening but it causes uterine contractions which cause hyperstimulation of the uterus leading to fetal distress. So, the search continues for an ideal ripening agent that cause cervical ripening without stimulating uterine contractions and reducing the risk of tachysystole.

Materials and Methods: In this Open labelled randomized controlled trial 80 patients requiring induction of labour with an unfavourable cervix (Bishop score ≤ 6) were included. They were randomly divided into two groups by using computer generated random number tables. In group I, 20mg of isosorbide mononitrate and 25mcg misoprostol was given intravaginally in the posterior fornix 4 hours apart maximum 8 doses or till Bishop>6. In group II induction was done with misoprostol alone 25mcg was given 4 hourly maximum upto 200mcg or Bishop>6 which ever is earlier. Augmentation was done in both the groups either by artificial rupture of membranes or Oxytocin drip. Labour was monitored by WHO PARTOGRAPH.

Results: In both the groups primigravida subjects were more in number (45% in group I and 42.5% in group II). Most common indication for induction at term was post dated pregnancy. Both groups were found to be comparable in terms of pre induction Bishop score. The mean Bishop score at 12 h was significantly higher in the group I (7.1 ± 1.9) than the group II (4.8 ± 2.3); p value <0.001. The caesarean rate was less in group I but the result was not statistically significant (p=0.11). Most common indication for caesarean section was acute fetal distress in both the groups (82.35% in group I and 65% in group II). Neonatal outcome was comparable in terms of APGAR score and admission in NNU/NICU. There were minimal side effects in both the groups with no maternal and fetal compromise.

Conclusion: Induction of labour with Isosorbide Mononitrate and Misoprostol compared to misoprostol alone to assess safety and efficacy of isosorbide mononitrate in pre-induction cervical ripening.

Key Word: Cervical ripening, Isosorbide mononitrate, Prostaglandins, Bishop score

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I. Introduction

Induction implies stimulation of uterine contractions before the onset of labour with or without ruptured membranes. When the cervix is closed and unefaced labour induction will always commence with cervical ripening; a process that generally employs prostaglandins to soften and open the cervix. Cervical ripening usually begins prior to the onset of labour and is necessary for cervical dilatation and subsequent passage of the fetus. Cervical ripening is commonly used to enhance the rate of successful labour induction. Induction of labour with an unripe cervix is the main cause of induction failure. There are various
pharmacological drugs used for cervical ripening and induction like PGE1 and PGE2. Prostaglandins cause uterine contractions which cause hyperstimulation of the uterus leading to fetal distress. So, the search continues for an ideal ripening agent that cause cervical ripening without stimulating uterine contractions and reducing the risk of tachysystole which may reduce the incidence of meconium stained liquor and fetal heart rate abnormalities.

During the recent years, Nitric oxide donors (NODs), like isosorbide mononitrate (IMN), has been studied as an agent for pre induction cervical ripening with less adverse effects. In addition, NODs have a relative relaxant effect on the uterine myometrium. Thus, these are not expected to cause uterine hyperstimulation in contrast to prostaglandins. Isosorbide mononitrate causes increase in cyclo-oxygenase-2 which induces endogenous prostaglandin production in the cervix and also leads to cervical ultrastructural rearrangement that is similar to spontaneous onset of labour. Isosorbide mononitrate is an FDA approved CATEGORY C drug; IT IS COST EFFECTIVE and easily available in the market.

Thus, we aim to study vaginal isosorbide mononitrate with misoprostol compared to misoprostol alone after randomization to assess safety and efficacy of isosorbide mononitrate in pre-induction cervical ripening and to assess whether there is any reduction in the required number of doses of misoprostol when used in cervix that is primed with isosorbide mononitrate which may reduce the dose related adverse effects of misoprostol.

II. Material And Methods

This open labelled randomized control trial was carried out on patients of Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh from june 2017 to june 2018. A total 80 pregnant females were included in this study.(10)

Study Design: open labelled randomized control trial

Study Location: This was a tertiary care teaching hospital based study done in Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh, India.

Study Duration: June 2017 to June 2018

Sample size: 80 patients.

Sample size calculation: 80 pregnant women as per the formula

\[ N = 16 \frac{\sigma^2}{d^2} + 1 \pm 20\% \text{ contiguity in each group.} \]

Subjects & selection method: The study population was drawn from Antenatal Clinic (ANC Clinic) who presented to Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh from june 2017 to june 2018. Patients were divided into two groups (each group had 40 patients) using computer generated random number tables.

Group I received 20mg of isosorbide mononitrate and 25mcg misoprostol intravaginally in the posterior fornix 4 hours apart upto maximum 8 doses or till Bishop>6.

Group II received misoprostol alone 25mcg was given intravaginally in the posterior fornix 4 hourly maximum upto 200mcg or Bishop>6 whichever is earlier.

Inclusion criteria:
1. Singleton pregnancy at term in cephalic presentation.
2. Intact membranes

Exclusion criteria:
1. Parity (≥ 4)
2. Bishop score >6.
3. Rupture of membranes; chorioamnionitis.
4. Previous caesarean section, or any other type of uterine surgery like myomectomy).
5. Malpresentation.
6. Multiple pregnancy.
7. Maternal medical disorder.
8. Contracted pelvis.

Procedure methodology

80 women requiring indicated induction of labour with an unfavourable cervix (Bishop score ≤ 6) were included in the study. Cases were selected from antenatal clinic (ANC OPD) and patients admitted in the hospital. They were randomly divided into two groups by using computer generated random number tables. Written and informed consent was obtained, they were enrolled in the study. This study was approved by the ethics committee of Faculty of medicine King George Medical University.
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among primiparous to multiparous. The most common indications for caesarean section in both groups was acute fetal distress (77.7%). The number of failed inductions were almost equal in both groups. Comparable side effects were present in both the groups (table 4).

Fetal outcome was four newborn (10.8%) in group 2 had an Apgar scores ≤7 compared with one newborns (2.5%) in group 1 (p value=0.139); though the NNU/NICU admission were none in Group I ;2newborn in group 2 were shifted to NNU;and none to NICU. Neonatal Outcome of Study Population in terms of Birth weight was comparable in both groups (grp I 2.72±0.31 (n=40) Grp II 2.70±0.44 (n=40) p valvu 0.792 NS(table 5)

IV. Discussion

Induction of labour in women with unripe cervix is frequently prolonged and very often unsuccessful, resulting in caesarean delivery. Studies have established that prelabour cervical status highly correlates with the inducibility of labour. In this study the two groups were comparable in their demographic profile, preinduction Bishop score and indication for induction of labour. The time from start of medication to complete vaginal delivery was non significant between group I (17.95±9.16 vs grp II22.30±24.39); p value=0.294 which was against the study done by Elsokary et al. 2015 who demonstrated significant reduction with IMN and time of 19.56 hrs (p value <0.001) and also in discordance with Ahmed T. Soliman et al. 2013 who demonstrated a time of14.8±6.2 hrs (p value <0.001). The difference in the results could be due to the dose of IMN used in the present study(20 mg) when compared to other two studies (40 mg). A less dose was considered in view of synergistic action of misoprostol when used with IMN in grp I patients.

In present study there was significant reduction in the number of repeat doses required for cervical ripening(Bishop>6) between grp I and grp II (3 doses vs 4 doses p value 0.02 Significant) signifying that addition of IMN can decrease the net dose of PG’s when used in combination. In this study ,not much improvement was seen in the Bishop score after 8 hrs. However, significant change in the Bishop score was observed in my study after 12 hrs of start of induction (7.1±1.9 ) in study group1 comparing to group II 4.8±2.3 which was statistically significant p <0.001, which is in concordance with study done by Ahmed T Soliman where mean Bishop score at 6 h was significantly higher in the combination therapy (7.1 ± 1.9) and the misoprostol (6.8 ± 2.3) groups compared with the IMN group (6.1 ± 2.1, P = 0.02)

The need of oxytoxin for induction was less in Grp II as compared to Grp I (37.5% vs 15%) and the most common method to augement labour was combined ARM and oxytocin in both the groups which was comparable (50%vs 57.5% p value 0.5 NS ).this was in accordance with study done by Ramya Krishnamurthy as she also noted that the need for oxytocin was less in IMN group when compared to placebo group but not in harmony with study done by Abdul Razaq regarding oxytocin need there is significant decrease in use of oxytocin for initiation or augmentation of labour .

In both the groups there was no statistically significant difference between both the groups as regard to birth weight, Apgar score, and need for NNU/NICU admissions. The result were comparable with other studies Elsokary et al. 2015, Ahmed T. Soliman et al. 2013 and Elmishly et al. 2016.

In the present study , not many patients complained of headache as compared to the previous studies where headache was the major side effect as shown in a study done by Elsokary et al. 2015 where incidence of headache was 46.7% in IMN group 41 Abdellah et al. 1997 found no significant difference between the two groups in the incidence of uterine hypersystole or tacyystole , which was similar to the present study.

V. Conclusion

The present study suggests that both intravaginal misoprostol and combination of isosorbide mononitrate and misoprostol are safe and effective modes of labour induction. Isosorbide mononitrate and misoprostol is more effective than misoprostol alone in terms of post induction Bishop Score, shorter induction to active phase interval and no of repeat doses.

References

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[10]. Elmahdy M 1*, Galal H 1, Marsafawi A El I, Amin2 N 1 Obstetrics and Gynecology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt 2 Ministry of Health Hospitals, Alexandria, Egypt Received 10 June 2016; accepted 2 July 2016; published 5 July 2016.

**Table 1** Pre induction bishop score and post induction scores at 8 and 12 hours.

<table>
<thead>
<tr>
<th></th>
<th>GROUP I (ISM+Misoprostol) (n=40)</th>
<th>GROUP II (Misoprostol) (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre induction Bishop score</td>
<td>3.1±1.1</td>
<td>3.4±1.0</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td>t=1.342</td>
</tr>
<tr>
<td></td>
<td>GROUP I</td>
<td>GROUP II</td>
<td>p</td>
</tr>
<tr>
<td>After 8 hrs(2 doses)</td>
<td>4.1±1.2</td>
<td>3.8±1.3</td>
<td>1.072</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td>p=0.287</td>
</tr>
<tr>
<td>After 12 hrs(3 doses)</td>
<td>7.1±1.9</td>
<td>4.8±2.3</td>
<td>4.876</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2** Induction to delivery time interval. Time to onset of active labour after induction and from augmentation to onset of 2nd stage of labour was significantly less in Grp I as compared to Grp II.

<table>
<thead>
<tr>
<th></th>
<th>GROUP I Mean±SD(Hr)</th>
<th>GROUP II Mean±SD(Hr)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME FROM START OF MEDICATION TO ONSET OF ACTIVE LABOUR</td>
<td>11.1±4.8</td>
<td>14.6±2.4</td>
<td>t=4.125</td>
</tr>
<tr>
<td>TIME FROM ARM/ OR OXYTOCIN TO ONSET OF 2ND STAGE OF LABOUR (h)</td>
<td>6.1±1.5</td>
<td>7.9±1.5</td>
<td>t=5.367</td>
</tr>
<tr>
<td>TOTAL TIME FROM START OF MEDICATION TO DELIVERY (h)</td>
<td>17.95±9.16</td>
<td>22.30±24.39</td>
<td>t=1.056</td>
</tr>
</tbody>
</table>

**Table 3.** Comparison of Number of doses required in Grp I and II showed that significant patients in Grp I were induced at 3rd dose as compared to 4th dose in Grp II.

<table>
<thead>
<tr>
<th>No. of doses required</th>
<th>GROUP I (n=40)</th>
<th>GROUP II (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 doses</td>
<td>12(30%)</td>
<td>11(27.5%)</td>
<td>0.6</td>
</tr>
<tr>
<td>3 doses</td>
<td>22(55%)</td>
<td>8(30%)</td>
<td>0.02</td>
</tr>
<tr>
<td>4 doses</td>
<td>4(10%)</td>
<td>16(40%)</td>
<td>0.10</td>
</tr>
<tr>
<td>≥5 doses</td>
<td>2(5%)</td>
<td>5(12.5%)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Table 4.** Comparison of side effects between both the groups.

<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th>GROUP I (n=40)</th>
<th>GROUP II (n=40)</th>
<th>t*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2</td>
<td>0</td>
<td>2.051</td>
<td>0.152</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2</td>
<td>3</td>
<td>0.213</td>
<td>0.644</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>0</td>
<td>0.613</td>
<td>0.314</td>
</tr>
<tr>
<td>Tachysystole</td>
<td>0</td>
<td>3</td>
<td>3.117</td>
<td>0.077</td>
</tr>
<tr>
<td>PPH</td>
<td>1</td>
<td>0</td>
<td>1.013</td>
<td>0.314</td>
</tr>
</tbody>
</table>

**Table 5.** Fetal outcome and neonatal outcome between the groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=40)</th>
<th>Group II (n=37)</th>
<th>Total (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>1</td>
<td>2.50</td>
<td>5</td>
</tr>
<tr>
<td>≥7</td>
<td>39</td>
<td>97.50</td>
<td>89.19</td>
</tr>
<tr>
<td>Birth Weight (Kg)</td>
<td>2.72±0.31 (n=40)</td>
<td>2.70±0.44 (n=40)</td>
<td>2.71±0.38 (n=40)</td>
</tr>
</tbody>
</table>

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